

their right to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications.

A marked up version of the amended paragraph showing the amendments is attached hereto as Appendix A. Matter that has been deleted is indicated by brackets and matter that has been added is indicated by double underlining.

The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

Claims 60, 65, and 70 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Without in any way conceding that nucleic acid probes comprising nucleotide sequences that encode for proteins or fragments thereof that are involved in the biosynthesis of tetracycline, oxytetracycline, puromycin, doxorubicin, taxol, chloramphenicol, nalidixic acid, mithramycin, novobiocin, vulpinic acid, usnic acid, kainic acid, podophyllotoxin, brevitorin, camptothecin, or artemisinin are not supported in the specification and for the sole purpose of expediting prosecution of this application, Applicants have canceled claims 60, 65, and 70.

In view of the foregoing, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Rejection Under 35 U.S.C. § 103 Is In Error

Claims 27, 28, 36, and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,004,788 (the '788 patent) and U.S. Patent No. 5,958,672

(the '672 patent). The Examiner alleges that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make the libraries of the Applicants' invention because the '788 and '672 patents claim enzyme products and methods of identifying enzyme products made from libraries of instant claims 27, 28, 36, and 43. Applicants respectfully disagree.

The instant application is a divisional application of U.S. Patent Application No. 08/738,944 filed November 24, 1996 (now U.S. Patent No. 5,783,431) which is a continuation-in-part application of U.S. Patent Application No. 08/639,255 filed April 24, 1996 (now U.S. Patent No. 5,824,485) which is a continuation-in-part application of U.S. Patent Application No. 08/427,244 filed on April 24, 1995 (the '244 application, now abandoned). As such, Applicants submit that the subject matter of the rejected claims 27, 28, 36 and 43 is entitled to the priority date of the '244 application which is April 24, 1995. Because the filing date for the '788 and '672 patents is July 18, 1995, Applicants submit that the '788 and '672 patents are not available as prior art for any purpose under 35 U.S.C. § 102 or § 103.

The subject matter of the rejected claims is supported by the following disclosures in the '244 application:

The '244 application discloses methods for generating metabolic pathways capable of functioning in foreign host cells. To this end, combinatorial gene expression libraries are created that contain DNA from at least one species of organism capable of producing at least one chemical substance or activity of interest. By introducing such libraries into host cells and allowing the expressed proteins to interact with host cell proteins, novel metabolic pathways could be created.

The libraries disclosed in the '244 application encompass the libraries claimed in the rejected claims. The '244 application discloses and claims gene expression libraries in which the subject DNA molecules used in its construction are from a plurality of species (see claim 3 and 16 as originally filed in the '244 application), and can be cDNA or genomic DNA (see page 11, line 35 of the '244 application). The '244 application contemplates that up to 1,000 different species can be represented in a single gene expression library (see the '244 application at page 10, lines 24-35).

The '244 application discusses the problem with microorganisms that cannot be grown in the laboratory and that may still be of interest (see *e.g.*, page 2, line 32 to page 3, line 29), and the utility of the gene expression libraries to circumvent this technical problem. In particular, the '244 application teaches that genome DNA is cloned into a gene expression library directly from sample organisms without *in vitro* cultivation (see *e.g.*, page 8, lines 9-20). The '244 application discloses that the subject DNA can be obtained from numerous sources, and that, in certain embodiments, marine bacteria in seawater can be used to construct the gene expression libraries (see the '244 application, page 4, lines 27-29; page 8, lines 8-9; and page 12, lines 11-12). The '244 application demonstrates this by using seawater collected from 200 miles offshore as a source for microorganism DNA (see *e.g.*, page 15, lines 1-4), and further teaches that the seawater used is a taxonomically diverse sample (see the '244 application, page 15, lines 5-7).

Once donor microorganism DNA has been isolated, the steps of library construction and introduction into host cells via vectors are similar in both the instant application and the '244 application. For example, the DNA insert is operably associated with a regulatory element (see, *e.g.*, page 4, lines 8-9 and on page 8, lines 28-30 of the '244 application). The construction of the combinatorial gene expression library of claim 27 is

disclosed in the '244 application at page 16, line 29 to page 17, line 8. In claim 28, there is a further requirement that the expression constructs contain randomly concatenated DNA. Support for concatenation of library insert DNA can be found in the '244 application on page 4, lines 20-24; page 17, lines 9-14; page 18, line 32 to page 20, lines 25; and page 21, lines 12-18.

In view of the foregoing, Applicants submit that the '244 application provides support for the rejected claims which are directed to combinatorial gene expression libraries comprising insert DNA that are derived from a plurality of species of organisms in an environmental sample and that are operably associated with gene expression regulatory regions.

Even assuming *arguendo* that the benefit of the priority date of the '244 application is not claimed, Applicants submit that neither the '788 patent nor the '672 patent renders obvious claim 28, and its dependent claims 36 and 43. According to applicable case law, to reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). The mere fact that references *could* be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01. In this instance, Applicants submit that neither of the cited U.S. patents suggests the use of or provides any motivation to use randomly concatenated DNA in the making of a gene library.

Both of PTO's references fail to teach or suggest each and every element of the rejected claims. As such, the references are not sufficient to establish a *prima facie* case of obviousness. Applicants respectfully request that the rejection of Claims 28, 36 and 43 under 35 U.S.C. § 103(a) be withdrawn.

In view of the foregoing, Applicants respectfully request that the Examiner withdraws the rejections under 35 U.S.C. § 103(a).

MISCELLANEOUS

Claims 30-34, 37-41, and 51-56 have been objected to as depending from a rejected base claim. Applicants believe that claims 27 are 28 are allowable for the reasons outlined above. As such, the objection to claims 30-34, 37-41, and 51-56 cannot stand and must be withdrawn.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: October 12, 2001

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